Patient Oriented Problem Solving (POPS) Case Report

A 62-year-old man with new-onset bullae

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ABSTRACT

Cutaneous blisters and/or bullae can occur in autoimmune disorders, infections, genetic diseases, and drug hypersensitivity. We present the case of a 62-year-old man with two autoimmune conditions who was admitted for antibiotic treatment of a lower extremity infection and suddenly developed a bullous rash. His physical examination was significant for tense, bullous lesions that involved his chin, palms, and inner thighs. Narrowing the differential diagnosis for patients with blistering skin lesions is imperative for timely and appropriate management.

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CASE PRESENTATION

Chief Concern

New-onset bullous rash.

History of Present Illness

A 62-year-old man with psoriasis and progressive multiple sclerosis that resulted in paraplegia was admitted for a gangrenous left lower leg, which, 1 week later, resulted in left knee disarticulation. He received piperacillin-tazobactam for 1 week and vancomycin for 2 days. Ten days after the first dose of these antibiotics, he again received vancomycin as a premedication for a cystoscopy scheduled the following day. Three hours later, he developed perioral tingling, lip swelling, and an erythematous rash, which then progressed to painful lesions on his palms and blisters in his mouth. The following day, the Allergy and Immunology Service was consulted. On evaluation, the patient had blisters on his face and inner thighs. He also reported pain in his mouth and odynophagia.

Medical History

The patient's medical history was significant for multiple sclerosis, psoriasis, type II diabetes mellitus, hypertension, peripheral vascular disease, and neurogenic bladder. He was taking baclofen, lisinopril, simvastatin, furosemide, and vitamin D at home, all of which he had been on for several years. He had no family history of skin problems or autoimmune conditions. He did not use intravenous or recreational drugs. He had no recent travel or sick contacts.

Physical Examination

The patient was afebrile, and all other vital signs were within normal limits. Significant findings included mild bilateral conjunctival injections, buccal mucosa ulcerations, lower lip swelling with desquamation, and multiple tense intact bullae on the chin below the lip. In addition, he had multiple tense intact bullae on the inner thighs bilaterally, tender nodular lesions on his palms (Fig. 1), and erythematous papular lesions on his lower arms bilaterally. Furthermore, there were small crusted blisters on his glans penis. There was no appreciable cervical, axillary, or inguinal lymphadenopathy. Hepatosplenomegaly was absent. The remainder of his physical examination was unremarkable.

Diagnostic Studies

Laboratory analysis revealed a white blood cell count of 5900/mm^3, a hemoglobin value of 11.3 g/dL, a hematocrit value of 33.1%, platelets of 293,000/mm^3, an absolute eosinophil count of 0, blood urea nitrogen level of 16 mg/dL, creatinine level of 0.7 mg/dL, aspartate aminotransferase value of 20 units/L, and alanine aminotransferase value of 37 units/L. On urinalysis, there was no protein or blood found. No abnormalities were noted on subsequent complete blood cell counts with differential, complete metabolic panels or urinalyses. The infectious workup was

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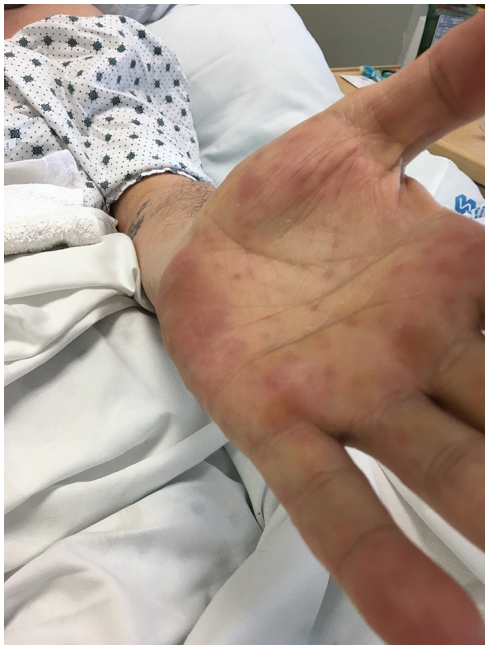

Figure 1. *Tender nodular lesions on the palms.*

unremarkable, including studies for hepatitis (A, B, and C), mycoplasma, and herpes simplex virus (1 and 2).

QUESTION 1

What is the differential diagnosis for bullous skin lesions?

QUESTION 2

Are there any additional diagnostic studies that would be helpful in arriving at the diagnosis?

DISCUSSION

The differential diagnosis for bullous skin disease includes viral infections, bullous impetigo, bullous pemphigoid, epidermolysis bullosa acquisita, dermatitis herpetiformis, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, linear immunoglobulin A (IgA) bullous dermatoses (LABD), diffuse fixed drug eruption, paraneoplastic pemphigus, pemphigus vulgaris, erythema multiforme, friction blisters, bullous diabeticorum, T-cell mediated contact dermatitis, or non–Severe Cutaneous Adverse Reaction (SCAR) T-cell mediated systemic drug eruptions (Table 1).

Given that the patient was not toxic appearing and was hemodynamically stable, there was low concern for infectious etiology. As such, blood cultures were deemed to be unnecessary. As described above, the primary team performed some infectious workups, results of which were negative. There is no specific laboratory workup available to diagnose SJS/TEN, although renal and/or hepatic involvement may be seen. However, as noted, this was not the case for our patient. Moreover, by using the Registry of Severe Cutaneous Adverse Reactions scoring system, our patient's score was <2 (including no eosinophilia and no signs of end-organ involvement on laboratory tests), excluding DRESS syndrome as the diagnosis. Skin biopsy is the criterion standard for the diagnosis of most forms of bullous skin disease.

Subsequently, the patient underwent punch biopsy; the specimen was significant for subepidermal bulla with fibrin, mild superficial perivascular chronic inflammation without epidermal necrosis, and linear IgA deposition along the dermoepidermal junction under direct immunofluorescence (DIF) (Fig. 2). At this time, a diagnosis of vancomycin-induced LABD was made. In addition to discontinuing the offending agent, the patient was treated with a 10-day prednisone taper, along with topical triamcinolone. He exhibited improvement of his existing lesions within 2 days of initiation of treatment, and no interval development of new lesions.

Vancomycin is a frequently used antibiotic that has been associated with a number of adverse effects, including nephrotoxicity, ototoxicity, neutropenia, thrombocytopenia, red man syndrome, and vasculitis. Hypersensitivity reactions have also been reported, including anaphylaxis, fixed drug eruptions, SJS, and DRESS syndrome.[1,2] Another form of drug hypersensitivity reaction is LABD. LABD is a rare autoimmune skin blistering disease in which autoantibodies bind to antigens in the skin and mucous membrane. It is characterized by linear deposition of IgA at the dermoepidermal junction.[3,4] This can be both drug-induced or idiopathic.[3,5–7] LABD has an incidence of 0.2 to 2.3 cases per million individuals per year, and occurs in both adults (generally ages > 60 years) and children (onset ~4.5 years old).[3,8] The inciting factor is usually unknown, but drug exposure has been identified as a precipitating factor, with vancomycin most frequently reported.

Other medications that have been implicated in LABD include other antibiotics, nonsteroidal anti-inflammatory drugs, lithium, amiodarone, furosemide, and captopril.[9] Of note, piperacillin-tazobactam has also been implicated in LABD.[10] Although our patient also received piperacillin-tazobactam, this was ultimately believed to be the less likely culprit agent, given the temporal relationship between the second administration of vancomycin and the subsequent development of symptoms. Thus, he was deemed vancomycin-allergic only, as to not limit his potential antibiotic options in the future. Although LABD can occur within 24 hours of vancomycin administration and unrelated to trough levels,[11,12] we postulated that he likely had circulating antigen specific IgA already, which resulted in the expedited reaction on re-exposure to

Table 1 **Differential diagnosis for bullous skin disease**

Disease	Characteristic Features	Mucosal Involvement
Bullous impetigo[29]	Superficial skin infection caused by *Staphylococcus aureus;* presents with vesicles that enlarge rapidly to form bullae that burst and become covered with honey-colored crust	May occur
Bullous pemphigoid[30]	Chronic autoimmune disorder with urticarial plaques and tense bullae on the trunk and flexural and intertriginous areas	Rare
Epidermolysis bullosa acquisita[31]	Rare, acquired, chronic condition with subepidermal blistering over the extensor aspects of the elbows and dorsal aspects of the hands and feet	May occur
Dermatitis herpetiformis[32]	Intensely pruritic, chronic, autoimmune, papulovesicular cutaneous eruption associated with celiac disease; presents with clusters of erythematous, urticarial lesions, vesicles, papules, and bullae; usually symmetric distribution on extensor surfaces	Rare to none
SJS/TEN[33]	Severe cutaneous hypersensitivity reactions with macules that spread quickly and coalesce, and lead to epidermal blistering, necrosis, and sloughing; often medication induced (sulfa drugs, antiepileptics, and antibiotics most common); SJS < 10% body surface area involved, and TEN > 30% body surface area involved	Very common (90% of cases)
Linear IgA bullous dermatosis[8,14–16]	Rare, autoimmune, skin blistering disease manifesting as cutaneous or mucosal lesions described as tense bullae; can involve the trunk, face, genitalia, perineum, lower abdomen, extensor extremities, hands, feet, and inner thighs	Common
Diffuse fixed drug eruption[34]	Type IV hypersensitivity reaction with recurrent lesions at identical sites on each exposure to an offending medication; characterized by well-demarcated red or brown patches, edematous plaques with or without bullae and post–inflammatory hyperpigmentation	Can be involved
Paraneoplastic pemphigus[35]	Rare autoimmune blistering disease associated with various malignancies, such as leukemias	Common
Pemphigus vulgaris[36]	Uncommon, potentially fatal, autoimmune disorder with intraepidermal flaccid blisters and/or bullae, and widespread, extensive erosion	Usually involved
Erythema multiforme[37]	Inflammatory reaction with target skin lesions on the distal extremities (often the palms and soles) as well as the face and trunk	May occur
Friction blisters[38]	Intraepidermal blisters that occur after prolonged exercise, resulting in trauma-induced separation within the epidermis, often over the feet	None
Bullous diabeticorum[39]	Rare, spontaneous, noninflammatory, blistering condition of unknown etiology in the setting of diabetes mellitus, usually involving the acral areas and lower extremities	None
T-cell mediated contact dermatitis[40]	Acute skin inflammation caused by irritants or allergens; the main symptom is pruritus, with skin changes, including erythema, blistering, and ulceration, usually on or near the hands but can occur on any exposed skin surface	Minimum to none

SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

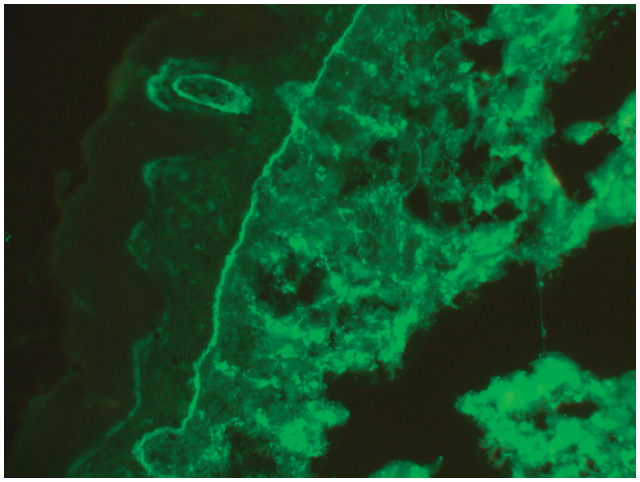

Figure 2. *Linear IgA deposition along the dermoepidermal junction under DIF.*

vancomycin. The pathogenesis of LABD is characterized by acquisition of IgA antibodies, which target basement membrane zone antigens involved in epidermal-dermal adhesion.[13] In drug-induced LABD, implicated drugs may cause an autoimmune response *via* cross-reaction with target epitopes, altering the conformation of epitopes, or exposing previously sequestered antigens to the immune system.[3]

Clinically, this disease manifests as cutaneous lesions, mucosal lesions, or both.[8,14–16] The cutaneous lesions develop acutely as tense bullae, typical of subepidermal blister formation. New blister formation occurs at the periphery of resolving lesions and results in an annular appearance, described as a "string of pearls." Lesions tend to be widespread and can involve the trunk, face (particularly the perioral area), genitalia, perineum, lower abdomen, extensor extremities, hands, feet, and inner thighs. Mucosal lesions can present as erosions or ulcers, which occur in up to 80% of adults and 3–64% of children. Involvement of the oral and ocular mucosa is most commonly seen, but involvement of the nose, genitalia, pharynx, larynx, anus, and esophagus have also been reported. Patients commonly experience pruritus, which may be severe.[17]

The lesions of drug-induced LABD resemble those of drug eruptions, *e.g.*, SJS/TEN, with large erosions and a positive Nikolsky sign (lateral pressure to the skin results in dislodgement of epidermis and extension of the blister).[18,19] Symptoms begin within 1 month of drug initiation, with resolution several weeks upon cessation of the offending agent.[8,20] Re-exposure to the offending agent may result in rapid recurrence of blisters. Demonstration of linear deposits of IgA along the basement membrane zone via DIF remains the criterion standard of diagnosis. However, serologic assays (IgA [or IgG] autoantibodies to basement membrane zone antigens Ladinin-1, Bullous Pemphigoid 180-non-collagenous16A and Bullous Pemphigoid 230) could support the diagnosis when a biopsy is not feasible or DIF results are negative.[21]

Data on treatment are limited. The mainstay of management in cases of drug-induced LABD is to discontinue the offending agent. As for idiopathic LABD, medical therapy with dapsone, an immunomodulatory sulfone, is considered first-line therapy.[14] Sulfonamides, *e.g.*, sulfapyridine, are considered second-line therapy. Other therapies include topical corticosteroids (may be sufficient in mild or localized LABD) as well as colchicine.[22,23] For severe or refractory disease, systemic glucocorticoids, mycophenolate mofetil, cyclosporine, intravenous immunoglobulin, systemic antibiotics, or tetracycline and nicotinamide may be used.[22,24,25] Treatment for idiopathic LABD is usually tapered off after several weeks of complete remission, whereas drug-induced LABD generally subsides with cessation of the offending agent. Idiopathic LABD can persist for months to years before spontaneous resolution; it can also recur but resolves in most children before puberty. With drug-induced LABD, new lesion formation ceases within 3 days of drug removal, with complete resolution within several weeks.[19,26–28]

Final Diagnosis

Vancomycin-induced LABD.

CONCLUSION

Given the timing of symptom development, our case highlights that LABD can occur either within just a few hours of vancomycin administration or that re-exposure to the drug results in a very accelerated reaction. We suspect the latter for our patient. In addition, our case also provides further support to the speculation that comorbidities and/or infection can serve as cofactors in the pathogenesis of drug-induced LABD.[3] Ultimately, it is crucial to identify this potentially life-threatening hypersensitivity reaction to enable both timely and appropriate management and/or treatment.

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